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PANDE, SUCHIRA	
ART UNIT	PAPER NUMBER
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/791,502	KRAMER ET AL.	
	Examiner	Art Unit	
	SUCHIRA PANDE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 2, 2008 has been entered.

Claim Status

2. Claims 1-16 are cancelled. Applicant has amended base claim 17. Currently claims 17-37 are pending and will be examined in this action.

Amendment to Specification changes Priority

3. Applicant has requested that the specification be amended by adding two paragraphs just before Summary section of the instant application. This amendment to specification adds additional new matter to the instant RCE application. Accordingly the instant application which is an RCE will now be entitled to the new priority date of January 2, 2008, the filing date of RCE when the specification was amended to add the two new paragraphs to the previously filed specification.

Response to arguments against rejection over Bruchez, Jr. et. al. (US Pat. 6,500,622) in view of Bonnet et al. 1999 under 103(a)

4. Applicant's arguments with respect to claims 17-37 have been considered but are moot in view of the new ground(s) of rejection. Applicant has amended the base claim

17. Previously cited art does not address the new limitations that have been added hence new grounds of rejection are being introduced.

5. Since previously cited art does not teach the base claim, accordingly the previous rejection of claims 23 and 32 over art cited to reject base claim 17 (in previous office action) further in view of secondary reference Bonnet et al. (1999) is no longer valid. Hence this rejection is being withdrawn.

Claim Interpretation

6. The claims are interpreted in the following way::

The term "capture probe" has not been defined in the specification. In one embodiment unlabeled hybridization probes are called capture probes. Therefore any probe can serve as capture probe.

Applicant has not defined "controllable" in the specification. Examiner is broadly interpreting that any change structural, physical or chemical that occurs is due to an alteration of some underlying conditions and hence is "controllable".

Applicant has not defined planar and linear array. In absence of any specific requirement following interpretation is being used: An array is distributed on a planar surface hence any array will be a planar array. Furthermore a line is a distance between two points hence any array will have two points so the probes distributed between any two points will represent a linear array.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 17- 22, 24-31, and 33-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al. (US Pat. 6,680,377 B1 issued January 20, 2004 with priority back to May 14, 1999) in view of Liu et al. (2000) Analytical Biochemistry 283: 56-63; Lizardi et al. (US pat. No 5,312,728 issued May 17, 1994) and Chee et al. (WO 01/46675 A2 published 28 June 2001, provided by Applicant in the IDS submitted with the amended claims).

Regarding claim 17, Stanton et al. teach: *a hybridization assay for at least one of a multiplicity of nucleic acid sequences in an analyte* (see col. 5 lines 31-35 where simultaneous detection of one or more target molecule is taught. Thus Stanton et al. teach *at least one of a multiplicity of sequences in an analyte. See col. 4, lines 1-5* where contacting the sample to the aptamer beacons is taught, such that **any** target molecules in sample can bind to corresponding binding regions of the aptamer beacon

is taught. Thus by teaching any target sequence Stanton et al. teach *nucleic acid sequences as target sequences.* Also see col. 3 lines 55-61 where Stanton et al. teach the aptamer beacons can comprise RNA, DNA. Both these types (DNA or RNA) of aptamers will bind their corresponding target nucleic acid sequences)

comprising the steps of:

*(a) contacting said analyte with a mixture of encoded microcarriers (*see col. 3. lines 65-67 and col. 4 lines 1-7 where aptamer beacons bound to solid support, such as particles (microcarriers) are taught. By teaching contacting the sample to beacons bound to particles, Stanton et al. teach *contacting said analyte with a mixture of encoded microcarriers having immobilized on their surfaces*

(ii) a coding scheme comprising a plurality of signaling hairpins (see col. 2 lines 41-56 where signaling hairpins are taught) *that are not capture probes for said at least one sequence* (note the beacons taught by Stanton et al. are not capture probes and are directly attached to the solid particle) *comprising quenched, fluorophore-labeled hairpin molecules each comprising an interacting affinity pair separated by a linking moiety, one member of said affinity pair having bound thereto at least one quenched fluorophore, wherein interaction of the affinity pair is disruptable to unquench said at least one fluorophore* (See col. 12 lines 53-61) *by a controllable physical or chemical change in a condition of its environment* (see col. 19 lines 17-26 where concentrations from low to high are taught as a controllable physical change),

wherein the disruption of the interaction of at least one affinity pair occurs at a first level of said condition and the disruption of the interaction of at least another affinity

*pair occurs at a second level of said condition (*see col. 25 lines 37-42 where varying thrombin concentration was used as a condition to disrupt the interaction of different aptamer beacons. Hence one concentration of thrombin is akin to first level of condition and another concentration of thrombin is akin to second level of condition that results in disruption of different affinity pair beacons),

and wherein said disruptions are optically differentiable (the changes in fluorescence intensity are measured see Table 1 col. 25 lines 55-60 thus indicating that they are optically differentiable) ,

*and wherein the coding scheme for identifying individual microcarriers in said mixture comprises a combination of multiple spectrally differentiable fluorophores (*see col. 13 lines 1-5 and lines 49-51 where multiple fluorophores are taught. These multiple fluorophores are spectrally differentiable—see col. 15 lines 20-39) *and multiple affinity pairs disruptable at detectably different levels of said condition* (see col. 4 lines 55-61 where multiple aptamers are taught that bind different enantiomers of target molecule---thus each enantiomer of target here represents different level of said condition that disrupts multiple affinity pairs) also see col. 25 Table 1 where different affinity pairs under column labeled Aptamers are shown in left and they are disruptable at detectable different levels as indicated by different fluorescence intensity measured by addition of thrombin (said condition));

(b) forming a distributed array (see col. 3 lines 51-52 and col. 4 lines10-11 where distributed planar array is taught) *of said microcarriers;*

Regarding claim 18, Stanton et al. teaches: *wherein said interacting affinity pair comprises complementary oligonucleotide sequences hybridized to one another* (see Fig. 2).

Regarding claims 19 and 20, Stanton et al. teaches *wherein said mixture of signaling hairpins includes at least three affinity pairs* (see col. 5, lines 31-52 where plurality of different species of aptamer beacons are taught—by teaching plurality Stanton et al. teaches *at least three affinity pairs*—claim 19 and *from three to eight affinity pairs*—claim 20).

Regarding claim 21, Stanton et al. teach *wherein steps (c) and (d) include decoding all microcarriers* (see col. 5 lines 5-6 where simultaneous detection of a plurality of target molecules is taught. This teaching requires that all particles—microcarriers be decoded.

Regarding claim 22, Stanton et al. teach *wherein said linking moiety comprises an oligonucleotide sequence* (see Figure 2 where aptamer molecular beacon is taught as a probe this molecule contains linking moiety, which is an oligonucleotide—see col. 9 line 2 where deoxyribose aptamers are taught).

Regarding claim 26, Stanton et al. *teach wherein a quencher is attached to the complementary oligonucleotide sequence not bearing the at least one fluorophore* (See col. 13 line 5 where DABCYL is taught as a quenchable dye that is attached to the complementary oligonucleotide sequence not bearing the at least one fluorophore—see Fig. 4B absorbing moiety marked 52 shown as triangle).

Regarding claim 33, Stanton et al. *teach the step of decoding includes disrupting said affinity pair by addition of a denaturant* (see col. 28 lines 1-12 where different concentrations of monovalent and divalent salts are taught. Since salts affect stability of affinity pairs hence by teaching different concentrations of salt Stanton et al. teach denaturant agents).

Regarding claim 17, Stanton et al. do not teach following:

Regarding claim 17 Stanton et al. do not explicitly recite the term "encoded micro carriers" in step a)

(i) a capture probe for said at least one sequence. The aptamer beacons of Stanton et al. are directly bound to the solid surface of the glass or particles. (See col. 3 lines 43-50). Hence no capture probes are used.

(c) determining which microcarriers have capture probes hybridized to said at least one nucleic acid sequence of said analyte; and

(d) optically decoding the microcarriers having hybridized capture probes to identify said at least one nucleic acid sequence.

Regarding claim 17, Liu et al. teach *(i) a capture probe for said at least one sequence*. (See abstract where use of biotin labeled ssDNA to immobilize Molecular Beacon MB—signaling hairpins on to solid optical fibers using avidin-biotin binding is taught. Hence the biotin labeled ssDNA serves the purpose of capture probe. Here capture probe is covalently linked to MB signaling probe.).

(d) optically decoding the optical fibers having hybridized capture probes to identify said at least one nucleic acid sequence. (see page 58 last par.--hybridization studies with immobilized molecular beacon where optical decoding is taught).

Regarding claim 37, Liu et al. teach wherein said capture probe is a molecular beacon probe (see page 57 last par. where biotinylated capture probe taught is a molecular beacon probe) .

Regarding claim 17, Liu et al. do not teach use of microcarriers. The optical fibers used by Liu et al directly have the molecular beacon (signal hairpin of instant invention) attached to the fiber via the biotin/avidin capture system. Hence design of the optical fiber detection system is such that step (c) is not taught in the method taught by Liu et al.

Regarding claim 17, Lizardi et al. teach *(i) a capture probe for said at least one sequence*. (See col. 9 line 66 where capture probe is explicitly taught. Also see col. 1, lines 36-58)

(c) determining which microcarriers have capture probes hybridized to said at least one nucleic acid sequence of said analyte (see col. 9 lines 64-66 where probes hybridized to targets are separated from unbound probes through use of capture probes is taught. Solid beads---microcarrier are taught by Lizardi and they teach binding the capture probe via biotin to streptavidin that is covalently linked to solid beads);

Regarding claim 17, Chee et al, explicitly teach use of a mixture of encoded microcarriers (see Page 4, lines 18-22 and page 5, lines 15-18).

Regarding claim 17, Chee et al, also teach beads containing capture probes (see page 9, line 11).

Regarding claim 21, Chee et al, teach wherein steps (c) and (d) include decoding all microcarriers (see page 25 lines 36-39 and page 26 lines1-2 where counting of beads is perfomed to provide positive and negative bead count. This inherently requires that all microcarries be decoded)

Regarding claim 24 and 30, Chee et al, teaches wherein forming the distributed array comprises immobilizing individual microcarriers at the ends of fibers in a fiber-optic bundle (see page 4, lines 2-6)

Regarding claim 25 and 34, Chee et al, teaches wherein steps c) and d) include flow cytometry (see page 23 line 15 where FACS is taught by teaching FACS Chee et al teach wherein steps c) and d) include flow cytometry).

Regarding claims 27-28 and 31, Chee et al. teach method of claim17. Claims 27 and 31 require that step (a) precede step (b) and claim 28 requires that step (b) precede step (a). Base claim 17 has been written using open language comprising. Hence to one of ordinary skill in the art it is obvious as to the order of sequence in which these two steps are conducted. This will depend on the type of assay being conducted. See MPEP 2144.04 IV c. 2144.04 Legal Precedent as Source of Supporting Rationale [R-1]. CHANGES IN SIZE, SHAPE, OR SEQUENCE OF ADDING INGREDIENTS. Changes in Sequence of Adding Ingredients. Selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results.

Regarding claims 29 and 35, Chee et al, teaches where distributed array is a planar array. (see page 8, line 26 where planar array is taught).

Regarding claim 36 Chee et al, teaches distributed array. As explained in claim interpretation by teaching a distributed array Chee et al inherently teach a linear array. Also Chee et al. teach sorting of beads by FACS. Here the beads are inherently sorted one after another i.e. in a linear manner hence the array of beads formed is a linear array.

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of Liu et al.; Lizardi et al. and Chee et al. in the method of Stanton et al. at the time the invention was made. The motivation to do so is provided by both Lizardi et al. and Chee et al.

Lizardi et al. state " a more recently developed form of bioassay that uses nucleic acid hybridization probes involves a second probe, often called a "capture probe".----A capture probe contains a nucleic acid sequence which is complementary to the target,----. The capture probe is provided with a means to bind it to a solid surface. Thus hybridization can be carried out in solution, where it occurs rapidly, and the hybrids can then be bound to a solid surface. One example of such a means is biotin.----Through biotin the capture probe can be bound to streptavidin covalently linked to solid beads. (see Lizardi et al. US pat. 5,312, 728 col. 1 lines 36-58). In view of this teaching one of ordinary skill realizes the advantage of using capture probes.

Method taught by Liu et al. is not very flexible because each fiber optic sensor has the MB probes that are immobilized directly on the fiber tip using biotinylated

capture probe. Effectively one such fiber optic fiber can be used to interrogate only one target at a time as its individually addressed (see page 60 last par). Using the method taught by Chee et al. one is able to increase the flexibility of the system in a facile manner.

Chee et al. state "array compositions that utilize microspheres or beads on a surface of a substrate, for example on a terminal end of a fiber optic bundle, with each individual fiber comprising a bead containing an optical signature------One drawback with the previous system is that it requires a set of unique optical signatures. While large sets of such signatures are available, for example by using different ratios of different dyes, it would be preferable to use decoding systems that do not rely on the use of sets of optical signatures. Accordingly it is an object of the invention to provide methods to allow decoding of bead arrays without relying solely on unique optical signatures" (see page 3 line 39-page 4 lines 1-8). Thus increasing the flexibility of the sensitive fiber optic sensors taught by Liu et al., due to use of encoded beads same fiber optic fibers can be used to interrogate many differently labeled beads.

10. Claims 23 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al. (US Pat No 6,680,377 B1); in view of Liu et al. (2000); Lizardi et al. (US pat. No 5,312,728) and Chee et al. (WO 01/46675 A2) as applied to claims 17-18 above in view of Bonnet et al. (1999) Proc. Natl. Acad. Sci. vol. 96: pp. 6171-6176 (cited by applicant in the IDS)

Regarding claims 23 and 32, Stanton et al.; in view of Liu et al.; Lizardi et al. and Chee et al. teach methods of claims 18 and 17 respectively but do not teach wherein

the step of decoding includes disrupting the hybridized affinity pairs by increasing temperature.

Regarding claims 23 and 32, Bonnet et. al. teaches wherein the step of decoding includes disrupting the hybridized affinity pairs by increasing temperature (see Table 1, page 6175 where probe target duplexes containing three mismatches A-A; C-A; and G-A is taught. The mismatch leads to change in melting temperature for dissociation of probe from target duplex. Perfect match TA has a melting temp of 42°C. While G-A mismatch dissociates at 28°C; A-A mismatch dissociates at 27°C and C-A mismatch dissociates at 23°C. This implies that at those three different temperatures the microcarrier containing those specific DNA molecules will become fluorescent and hence would be identified by Flow cytometery instrument capable of performing Fluorescent Activated Cell Sorting (FACS) analysis (taught by Chee et al. see above). Thus Bonnet et al. teaches step of decoding includes disrupting the hybridized affinity pairs by increasing temperature.

It would be *prima facie* obvious to one of ordinary skill in the art at the time of this invention to combine the affinity pairs taught by Bonnet et al. with the signaling affinity system taught by Stanton et al.; Liu et al.; Lizardi et al. and Chee et al.

The motivation to do so is provided by Chee et al. who teach decoding of array sensors with microspheres. Chee et al. teach decoding using pH titration in one embodiment (see page 27 lines 35-39 here optical signatures are generated using pH responsive dyes). Bonnet et al. teach that increasing temperature results in dissociation of strands based on the nature of the mismatch. Thus when temperature probes that

dissociate at different temperature are used in the invention of Stanton et al.; Liu et al.; Lizardi et al. and Chee et al. it will result in formation of microcarries (microspheres) carrying hairpins as signaling molecules that respond to variation in tempearture. In view of the above teachings one of ordinary skill in the art can logically reach the conclusion that instead of using pH titration as taught by Chee et al, one can use increasing temperature (as taught by Bonnet et al.) as a decoding scheme. The advantages of using such a scheme is explicitly provided by Chee at al. state "one drawback with the previous system (system of decoding---added by Examiner) is that it requires a set of unique optical signatures. While large sets of such signatures are available, ----, it would be preferable to use decoding systems that do not relay on the use of sets of optical signatures. Accordingly, it is an object of the invention to provide methods to allow decoding of bead arrays without relying solely on unique optical signatures" (see page 4, lines 10-15).

Conclusion

11. All claims under consideration 17-37 are rejected over prior art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637

March 19, 2008